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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/529,072

10/14/2005

Ralf-Holger Voss

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03/06/2009

SALIWANCHIK LLOYD & SALIWANCHIK

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EXAMINER

CHEN, SHIN LIN

ART UNIT

PAPER NUMBER

1632

MAIL DATE

DELIVERY MODE

03/06/2009

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/529,072	Applicant(s) VOSS ET AL.	
	Examiner Shin-Lin Chen	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 04 December 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-9, 12-23 and 27-30 is/are pending in the application.
- 4a) Of the above claim(s) 20-23, 27 and 28 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-9, 12-19, 29 and 30 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--------------------------------------------------------------------------------------|-------------------------------------------------------------------|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

Applicants' amendment filed 12-4-08 has been entered. Claims 1, 3 and 6 have been amended. Claims 10 and 11 have been canceled. Claims 29 and 30 have been added. Claims 1-9, 12-23 and 27-30 are pending. Claims 1-9, 12-19, 29 and 30 are under consideration.

It should be noted that Examiner for this application has been changed, any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-9 and 12-19 remain rejected and newly added claims 29 and 30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for method for producing a TCR complex wherein the alpha- and beta-chains of an MDM2(81-88)-specific TCR are used as alpha-chain and beta-chain, and wherein the Gly192 of the constant region of the alpha-chain and the Arg208 of the constant region of the beta-chain are exchanged by Arg 192 in the constant region of the alpha-chain and by Gly208 in the constant region of the beta-chain, does not reasonably provide enablement for method for producing any other heterodimeric specific wild-type or chimeric TCR having any antigen specificity, wherein any and all domains (i.e. extracellular, transmembrane and intracellular domains) of the TCR-complex has been modified by mutagenesis to obtain the sterically arranged groups (as claimed) on TCR chains.

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The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims and is repeated for the reasons set forth in the preceding Official action mailed 6-4-08. Applicant's arguments filed 12-4-08 have been fully considered but they are not persuasive.

Claim 1 has been amended to read on a method for providing a heterodimeric specific wild type or chimeric T-cell receptor (TCR) in a manner such that externally provided TCR-chains do pair and do not form mixed pairs with endogenous TCR-chains of T-cells and TCR functionality and stability is not impaired, and further recites specific amino acid residues for introducing sterically recessed group and sterically projecting group. Newly added claims 29 and 30 specify mutagenesis of the DNA molecule is in a TCR ecto-domain and TCR constant domain, respectively.

Applicants argue that the specification teaches how to make mutated TCRs, how to introduce them into cells, and how to test these TCRs for functionality. The introduced mutations are not random mutations but rather are rational design. Both human and murine have similar TCR structures and allows for inter-species design. Applicants cite Voss reference and argue that the claimed method can be used to modify a human TCR having specificity for gp100. A considerable amount of experimentation is permitted if it is merely routine screening (amendment, p. 12-13). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 6-4-08. The scope of the instant claims encompasses method for producing any heterodimeric specific wild-type or chimeric TCR with any antigen specificity, wherein any and all domains (i.e. extracellular, transmembrane and intracellular domains) of the TCR-complex has been modified by mutagenesis and the functionality and stability of the TCR

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is maintained. Although it was known how to make mutated TCRs, how to introduce them into cells and how to test TCR functionality, the state of the art at the time of filing was such that the TCR is the most intricate membrane receptor structures known in the art, wherein any mutation in the TCR-complex would cause unintentional conformational changes rendering the scope of invention as claimed highly unpredictable. It was unpredictable at the time of the invention whether the mutations, including reciprocal exchange, introduced to various TCR domains, including extracellular domain, variable domain, constant domain, connecting peptides, transmembrane domain and intracellular domain, would be able to maintain TCR functionality and stability. In instant case producing wild-type or chimeric TCR receptors specific to a particular antigen and to maintain its functionality and stability, wherein the first and second chain mutated to provide sterically arranged sites is not considered routine in the art and without sufficient guidance to a specific TCR structure associated with corresponding mutated sites designated on each TCR chain, the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. Further, the claims also encompass genetic modification of a cell in-vivo, therefore the invention falls in the realm of gene therapy in vivo. The state of the art of gene therapy in vivo was unpredictable at the time of the invention. One of the greatest challenges facing gene therapy is the efficient transfer and stable expression of transgene in appropriate tissues. Thus, one skilled in the art at the time of the invention would require undue experimentation to practice over the full scope of the invention claimed.

Conclusion

No claim is allowed.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Shin-Lin Chen, Ph.D.
/Shin-Lin Chen/
Primary Examiner
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